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EXAMINER	
DEVI, SARVAMANGALA J N	

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1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/761,498	MICHON ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13,15,16,18-37 and 39-66* is/are pending in the application.

4a) Of the above claim(s) *10,29-36,41-58 and 62-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-9,11-13,15,16,18-28,37,39,40,59-61 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01/20/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11122008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination under 37 C.F.R 1.114

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 11/12/08 has been entered.

Applicants' Amendments

2) Acknowledgment is made of Applicants' amendments filed 01/29/09 and 11/12/08 in response to the final Office Action mailed 05/19/08.

Status of Claims

3) Claims 14, 17 and 38 have been canceled via the amendment filed 01/29/09.

Claims 1, 15, 16, 18-21, 26-28, 37, 39 and 59-61 have been amended via the amendment filed 01/29/09.

New claim 66 has been added via the amendment filed 01/29/09.

Claims 1, 4-13, 15, 16, 18-37 and 39-66 are pending.

Claims 1, 4, 5, 8, 9, 11-13, 15, 16, 18-28, 37, 39, 40, 59-61 and 66 are under examination. The examination has been extended to the second and third polysaccharide or oligosaccharide species, meningococcus and *E. coli* K1 polysaccharide or oligosaccharide species and to the second protein species, diphtheria toxoid.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' information disclosure statement filed 11/12/08. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

7) The objection to claim 1 made in paragraph 31(a) of the Office Action mailed 05/19/08 is withdrawn in light of Applicants' amendment to the claim.

8) The objection to claim 16 made in paragraph 31(b) of the Office Action mailed 05/19/08 is withdrawn in light of Applicants' amendment to the claim.

Rejection(s) Moot

9) The rejection of claim 14 made in paragraphs 23 and 24 of the Office Action mailed 05/19/08 under 35 U.S.C. § 112, first paragraph, as containing new matter, is moot in light of Applicants' cancellation of the claim.

10) The rejection of claim 14 made in paragraph 27 of the Office Action mailed 05/19/08 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is moot in light of Applicants' cancellation of the claim.

11) The rejection of claim 14 made in paragraph 30(h) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

Rejection(s) Withdrawn

12) The rejection of claim 1 and the dependent claims 4, 5, 8, 9, 11-13, 15, and the rejection of claim 16 and the dependent claims 18-28, 37, 39, 40 and 59-61 made in paragraph 23 of the Office Action mailed 05/19/08 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the base claims.

13) The rejection of claim 59 made in paragraph 25 of the Office Action mailed 05/19/08 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the claim.

14) The rejection of claim 37 and the dependent claim 39 made in paragraph 26 of the Office Action mailed 05/19/08 under 35 U.S.C. § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the claims.

15) The rejection of claims 1, 4, 8, 9, 11-13, 15, 16, 18-28, 37, 39, 40 and 59-61 made in paragraph 27 of the Office Action mailed 05/19/08 under 35 U.S.C § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn in light of Applicants' amendment to the claims and/or the base claims.

16) The rejection of claims 25 and 40 made in paragraph 28 of the Office Action mailed 05/19/08 under 35 U.S.C § 112, first paragraph, as containing new matter, is withdrawn in light of Applicants' amendment to the base claim.

17) The rejection of claim 1 made in paragraph 30(a) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

18) The rejection of claims 1 and 16 made in paragraph 30(b) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

19) The rejection of claims 4, 5, 11, 12 and 15 made in paragraph 30(c) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

20) The rejection of claim 16 made in paragraph 30(d) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

21) The rejection of claim 26 made in paragraph 30(e) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

22) The rejection of claim 37 made in paragraph 30(f) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

23) The rejection of claim 39 made in paragraph 30(g) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

24) The rejection of claim 60 made in paragraph 30(h) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

25) The rejection of claims 4, 5, 8, 9, 11-13, 15, 18-28, 37, 39, 40 and 59-61 made in paragraph 30(i) of the Office Action mailed 05/19/08 under 35 U.S.C § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

26) The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

27) Claims 1, 16 and the dependent claims 4-9, 11-13, 15, 18-28, 37, 39, 40, 59-61 and 66 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, includes the limitations: N-acryloylated to comprise 'at least one N-acryloyl group' and 'the at least one N-acryloyl group of the polysaccharide or the oligosaccharide'. Claim 16, as amended, includes the new limitations: 'to replace at least one removed N-acetyl group with at least one N-acryloyl group' and 'the at least one N-acryloyl group of the N-acryloylated polysaccharide or the N-acryloylated oligosaccharide'. Note that the term 'at least one' has no upper limit. Applicants point to lines 10-15 and 20-23 of page 4, page 8, line 24 through page 9, line 7, and page 9, line 10 to page 11, line 25 of the specification for support to these amendments. However, these parts of the specification do not support the limitations 'at least one N-acryloyl group' of the polysaccharide or the oligosaccharide and for the replacement of 'at least one removed N-acetyl group with at least one N-acryloyl group'.

Claim 1, as amended, replaces the previous limitation 'a de-N-acetylated polysaccharide or an de-N-acetylated oligosaccharide' with the new limitation 'a polysaccharide or an oligosaccharide' wherein 'the polysaccharide or the oligosaccharide is natural'. Claim 16, as amended, includes the new limitation: 'a polysaccharide or an oligosaccharide' (see part A). Applicants point to lines 10-16 of page 9; lines 12-17 of page 6; page 7, line 24 to page 8, line 23; and lines 4-12 of page 11 of the specification and state that support for these amendments can be found therein. The limitation 'a polysaccharide or an oligosaccharide' encompasses non-isolated polysaccharide or oligosaccharide as present naturally on the surface of bacteria. While there is support in the original claim 16 for --an isolated-- polysaccharide or oligosaccharide, for example, from bacteria that is de-N-acetylated and N-acryloylated before conjugation, there is no descriptive support an immunogenic conjugate as claimed currently comprising a non-isolated polysaccharide or oligosaccharide from bacteria. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification as filed, for the new limitation(s), or remove the new matter from the claim(s). Applicants should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Lack of Enablement)

28) Claims 25 and 40 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;

- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a combination vaccine or a combination pharmaceutical composition comprising: (a) a pharmaceutically acceptable carrier; (b) a polysaccharide-protein conjugate or an oligosaccharide-protein conjugate comprising a N-deacetylated and N-acryloylated polysaccharide or oligosaccharide covalently attached to a protein via beta-propionamido linkage, or a polysaccharide-protein conjugate or an oligosaccharide-protein conjugate comprising an N-acryloylated polysaccharide or oligosaccharide conjugated to a bacterial protein via a lysine or a cysteine residue wherein the conjugate is 'immunogenic' and generates antibodies reactive against the bacteria from which the polysaccharide or the oligosaccharide was derived, as claimed in claims 1, 16 and 37; and (c) a second immunogen component selected from the group consisting of DTP, DTaP, tetanus-diphtheria, DTaP-Hib, DTaP-IPV-Hib, and combinations thereof. The examined polysaccharides or oligosaccharides are the *Streptococcus* Group B polysaccharide or oligosaccharide, *E. coli* K1 polysaccharide or oligosaccharide, and meningococcus polysaccharide or oligosaccharide species; DTaP second immunogenic component species; and tetanus toxoid or diphtheria toxoid protein species. The limitation 'polysaccharide' or 'oligosaccharide' is not limited to capsular polysaccharide or oligosaccharide, but encompasses lipopolysaccharide and lipooligosaccharide as well. This means that the claimed vaccine or composition comprising the de-N-acetylated and N-acryloylated *Streptococcus* Group B, *E. coli* K1, or the meningococcus polysaccharide or oligosaccharide conjugated to tetanus toxoid or diphtheria toxoid and further comprising the DTaP second immunogenic component or a combination second immunogenic component that comprises the DTaP is *required* to be 'immunogenic' capable of eliciting antibodies to each component in the combination vaccine or composition, wherein the antibodies elicited are required to be reactive against *Streptococcus* Group B, *E. coli* K1, or meningococci. However, there is a lack of showing that a de-N-acetylated and a N-acryloylated *Streptococcus* Group B polysaccharide- or oligosaccharide-tetanus toxoid or diphtheria toxoid conjugate, a de-N-acetylated and a N-acryloylated *E. coli* K1

polysaccharide- or oligosaccharide-tetanus toxoid or diphtheria toxoid conjugate, and a meningococcus polysaccharide- or oligosaccharide-tetanus toxoid or diphtheria toxoid conjugate as claimed in the instant invention can be combined with a second monovalent or multivalent protein component, such as, DTaP, or DTP, Td, DTap-Hib, DTaP-IPV-Hib, or combinations thereof, wherein the conjugate still remains optimally 'immunogenic' and produces antibodies reactive against *Streptococcus* Group B, *E. coli* K1, or meningococci. There is no showing that the instantly claimed conjugate when combined with one or more of any of the recited second component or combinations thereof, would retain its immunogenic function as a vaccine or pharmaceutical composition and would effectively elicit optimal GBS-specific, *E. coli* K1-specific, or meningococcus-specific immune response. This is important because the state of the art on combination vaccines at the time of the invention indicated the occurrence of potential interference by one or more added vaccine components. For instance, Barington *et al.* (*Infect. Immun.* 61: 432-438, 1993 – Applicants' IDS) taught that immunizations of conjugated polysaccharides and unconjugated (free) carrier protein (for example, TT in the instant case), lead to a non-epitope specific suppression of the antibody response not only to the carrier protein, but the polysaccharide as well. Corbel (*Biologicals* 22: 353-360, 1994 – Applicants' IDS) taught that the use of diphtheria and tetanus proteins as carriers for multiple polysaccharide conjugates may lead to epitope suppression of anti-polysaccharide responses (see abstract). Most importantly, the combining of DTaP and IPV or DTaP and IPV with a bacterial capsular polysaccharide-protein conjugate has been shown in the art to result in interference and a significant and pronounced reduction in immune response to IPV. For example, see page 1688 of Eskola *et al.* (*Lancet* 348: 1688-1692, 1996, of record), who concluded that '[t]he immunogenicity of all antigens must be tested before new combinations can be accepted for vaccination programmes …'. Eskola *et al.* used a conjugate produced by a method non-identical to Applicants' method and concluded that '[a]lthough all combinations proved safe, the poor immunogenicity of the Hib component when it was mixed with DTP-a in the two dose schedules studied here raises important questions about the immunonological mechanism of the interference seen and about its clinical relevance'. See first paragraph under 'Discussion'. In the instant case, Applicants claim that their claimed conjugate or vaccine is novel which uses a novel

method of conjugation. However, it is neither shown within the instant specification, nor is it predictable that the instantly claimed GBS conjugate species, *E. coli* K1 conjugate species, or meningococcus conjugate species comprising the beta-propionamido linkage when combined with a preparation containing DTaP or Hib conjugate, i.e., DTap-Hib or DTaP-IPV-Hib, or a combination thereof, would not produce interference or an immune response-suppressing effect on one or more vaccine components, but would retain its ability to be optimally 'immunogenic' capable of eliciting antibodies reactive with GBS, *E. coli* K1, or meningococci. Corbel further taught that the formulation of the combinations may present specific problems resulting from the interaction of the various components with each other and with the adjuvants and excipients (see page 353). Given the lack of evidence/guidance, the specific teachings in the state of the art on the potential interference by one or more added vaccine components, the poor polysaccharide immunogenicity, and the suppression of antibody response to the polysaccharide or the carrier protein, the unpredictability factor, the breadth of the claims, the lack of working examples, and the quantity of experimentation necessary, undue experimentation would have been required by one of ordinary skill in the art to practice the invention as claimed.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

29) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

30) Claims 1, 4-9, 11-13, 15, 16, 18-28, 37, 39, 40, 59-61 and 66 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and indefinite in the limitation 'derived', because it is unclear what is encompassed in this recitation. Does the process of 'deriving' encompass extraction, isolation, recombinant production, separation, purification, structural modification, or expression on a cell surface? If isolation is intended, it is suggested that Applicants replace the limitation 'either a polysaccharide or an oligosaccharide' in lines 3 and 4 of the claim with the limitation -- an isolated polysaccharide or an isolated oligosaccharide from a bacteria, yeast, or cancer cells--

and delete the limitations 'wherein the polysaccharide or the oligosaccharide is derived from bacteria, yeast, or cancer cells' from lines 13 and 14 of the claim.

(b) Analogous rejection and criticism apply to claims 4-7, 15, 37 and 39 with regard to the limitation 'derived'.

(c) Claim 16 is vague and indefinite in the limitation: 'derived' (see part A), because it is unclear what is encompassed in this recitation. Does the process of 'deriving' encompass extraction, isolation, recombinant production, separation, purification, structural modification, or expression on a cell surface? If isolation is intended, it is suggested that Applicants replace the limitation 'either a polysaccharide or an oligosaccharide' in lines 3 and 4 of the claim with the limitation --either an isolated polysaccharide or an isolated oligosaccharide from bacteria, yeast, or cancer cells-- and delete the limitations 'wherein the polysaccharide or the oligosaccharide is derived from bacteria, yeast, or cancer cells' from lines 5 and 6 of the claim.

(d) Claim 1 is indefinite, confusing, and appear to lack proper antecedent basis in the limitation: 'the polysaccharide or the oligosaccharide is covalently attached to the protein' (see lines 9 and 10). It is unclear where this limitation derives its antecedence from, because the earlier part of the claim recites two types of polysaccharides or oligosaccharides: the N-deacetylated and N-acryloylated polysaccharide or the N-deacetylated and N-acryloylated oligosaccharide; and a polysaccharide or an oligosaccharide. If the intention is to convey that the N-deacetylated and N-acryloylated polysaccharide or the N-deacetylated and N-acryloylated oligosaccharide is covalently attached to the protein, it is suggested that Applicants replace lines 11-14 of the claim with the limitations: --wherein the N-deacetylated and the N-acryloylated polysaccharide or the N-deacetylated and the N-acryloylated oligosaccharide is covalently attached to the protein ..... of the N-deacetylated and the N-acryloylated polysaccharide or the N-deacetylated and the N-acryloylated oligosaccharide--.

(e) Claim 4 is inconsistent with claim 5 in the non-italicized limitation 'Streptococcus'. To be consistent with the practice in the art, it is suggested that Applicants italicize the names of bacteria recited in the last line of claim 4.

(f) Analogous rejection and criticism apply to claim 39.

(g) Claim 16 is vague and indefinite in the limitation: 'about 50%' (see line 3) because it is unclear what range is encompassed in this limitation. Is a percentage of 50 $\pm$ 10 or 50 $\pm$ 20 encompassed within the scope of the limitation?

(h) Claim 59 is vague and indefinite in the limitation: 'about 95%', because it is unclear what range is encompassed in this limitation. Is a percentage of 95 $\pm$ 10 or 95 $\pm$ 20 encompassed within the scope of the limitation?

(i) Claim 37 is indefinite and confusing in the limitation 'antibodies reactive against the bacteria …', because it is unclear what precise functional property of the antibodies is encompassed in the limitation 'reactive against the bacteria'.

(j) Claims 4-9, 11-13, 15, 18-28, 37, 39, 40, 59-61 and 66, which depend directly or indirectly from claim 1 or 16, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

31) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (**b**) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

32) Claims 1, 4, 6-9, 11-13, 16, 18-21, 61 and 66 are rejected under 35 U.S.C. § 102(b) as being anticipated by Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992 – Applicants' IDS) as evidenced by Kabat *et al*. (*J. Exp. Med.* 164: 642-654, 1986 – Applicants' IDS).

The limitation 'about' in claims 16 and 18 is interpreted in this rejection as being equivalent to $\pm$ 5-10.

Pon taught polysaccharide or oligosaccharide-protein conjugates (i.e., oligosialic or polysialic conjugates) produced via Michael-type addition for use as a vaccine effective against *Escherichia coli* K1 and serogroup B *Neisseria meningitidis*. See page 14; Chapter 2; section 4.2.3.3 and Tables 4-5. The conjugates comprised an N-acryloylated sialic acid-containing K1 polysaccharide or oligosaccharide, isolated or synthesized, directly conjugated to a protein, such as, bovine serum albumin (BSA), a porcine IgG, or tetanus toxoid (TT) via the epsilon free amino

of a lysine residue by Michael-type addition, the same process by which the N-acryloylated polysaccharide of the instant invention is coupled to a protein as described under the first full paragraph under 'Detailed Description of the Invention' and sixth full paragraph under 'B. Preparation of beta-propionamido-linked Polysaccharide-protein Conjugates' of the instant specification. The conjugation was performed at a pH of above 9, i.e., 9.2, in borate buffer. Pon's Table 5-2 provides the *prima facie* evidence that colominic acid, with 31.1%, 45.6% or 57.7% (i.e., about 50%) de-N-acetylation, retained its antigenicity with H.46 antiserum. Furthermore, Table 5-3 depicts that N-acryloylated colominic acid showed strong precipitin bands with H.46 antiserum, an antibody that has been shown in the art to confer passive protection against *E. coli* K1 infection (see entire document, especially Table 1 of Kabat *et al.*). This is evidence that the N-acryloylated colominic acid in Pon's conjugate maintained its immunogenic and/or protective epitope and therefore was capable of reacting with the protective H46 antibody. Therefore, Pon's conjugate necessarily served as an immunogenic conjugate. See sections 4.2.3.3 and 2.2.1.3; pages 56 and 205; and Tables 5-2 and 5-3 of Pon. The conjugate was produced by a method comprising de-N-acetylating the polysaccharide or oligosaccharide using a de-N-acetylating base reagent, such as, NaOH, followed by N-acryloylating the de-N-acetylated polysaccharide or oligosaccharide with an acryloylating reagent, such as, acryloyl chloride and directly conjugating the resultant polysaccharide or oligosaccharide to the protein by Michael-type addition. See pages 39, 75 and 76; Table 2-3; sections 2.2.2.1 and 2.2.2.5; and section 4.2.3.3. Furthermore, the term 'recombinantly produced' in claim 9 represents a process limitation. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the

product of the prior art. In the instant case, Applicants have not shown the underlying structure of the prior art protein used in the conjugate differs from that of the instantly recited protein.

Claims 1, 4, 6-9, 11-13, 16, 18-21, 61 and 66 are anticipated by Pon.

33) Claims 1, 4, 6-9, 11-13, 22-24, 26-28, 37, 39, 61 and 66 are rejected under 35 U.S.C. § 102(b) as being anticipated by Jennings *et al.* (WO 96/40239 - Applicants' IDS).

Jennings *et al.* disclosed an *N*-acyl modified group B meningococcal sialic acid-containing polysaccharide or fragments thereof (i.e., oligosaccharides), for example, *N*-acryloylated group B meningococcal polysaccharide (GBMP) conjugated to a protein carrier, such as, tetanus toxoid, diphtheria toxoid, CRM197 and meningococcal outer membrane protein. The GBMP was first *N*-deacetylated and then treated with acryloyl chloride at a pH of 8.5 and then conjugated to tetanus toxoid at pH 7.5. The conjugate was purified and equilibrated in PBS (i.e., a pharmaceutically acceptable carrier). The conjugate composition or vaccine was used to immunize mice with or without adjuvants, such as, alum or stearyl tyrosine, wherein the conjugate induced group B meningococcal bactericidal antibodies (i.e., inclusive of IgG, IgM and/or IgA or combinations thereof that are reactive against group B meningococci). See Examples 1-4 and 7; page 6, lines 19-23; Tables 1-3; and pages 6-10. The *N*-acryloyl GBMP-tetanus toxoid conjugate, its use in immunizing mice with or without alum, and its ability to induce anti-group B meningococcal bactericidal and protective antibodies that are significantly less cross-reactive with the native GBMP, are described in Example 7 and Tables 1-3. Furthermore, the term 'recombinantly produced' in claim 9 represents a process limitation. When claims are drawn to a product-by-process, claims are not limited to the manipulations of the recited step(s), but only the structure implied by the steps. MPEP § 2113 states:

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process. *In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)* (citations omitted).

A product does not have to be made by the same process in order to be the same product, because a product is a product, no matter how it is claimed. Applicants have not shown that the alleged difference(s) in the process results in a product that is structurally different from the

product of the prior art. In the instant case, Applicants have not shown the underlying structure of the prior art protein used in the conjugate differs from that of the instantly recited protein.

Claims 1, 4, 6-9, 11-13, 22-24, 26-28, 37, 39, 61 and 66 anticipated by Jennings *et al.*

Rejection(s) under 35 U.S.C. § 103

34) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

35) Claims 59 and 60 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pon RA (*The Study of Polysialic acid Conjugates*. Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992 – Applicants' IDS) as applied to claim 1 or claim 16 above.

The teachings of Pon are explained above which do not disclose that the polysaccharide or the oligosaccharide in their conjugates is at least about or at least 95% N-acryloylated.

However, optimization of the degree of N-acryloylation of a de-N-acetylated polysaccharide or oligosaccharide was well within the realm of routine experimentation. No evidence is of record in the instant disclosure establishing that the recited percentage of at least about or at least 95% N-acryloylation is critical for the invention. It has been held legally obvious and within the routine skill in the art to optimize a result-effective variable. In the instant case, the percent N-acryloylation of the polysaccharide or oligosaccharide in the claimed conjugate is clearly a result-effective variable, and therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to vary or optimize the

percent N-acryloylation of the de-N-acetylated polysaccharide or oligosaccharide in Pons' conjugate to 95% or about 95% by routine experimentation to produce the instant invention.

Claims 59 and 60 are *prima facie* obvious over the prior art of record.

Remarks

36) Claims 1, 4-9, 11-13, 15, 18-28, 37, 39, 40, 59-61 and 66 stand rejected.

37) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

38) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (in USA or CANADA) or 571-272-1000.

39) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Robert Mondesi, can be reached on (571) 272-0956.

/S. Devi/
Primary Examiner
AU 1645

April, 2009